U.S.C. § 112, second paragraph, the rejection of claims 8, 9, and 11 under 35 U.S.C. § 112, first paragraph, and the rejection under 35 U.S.C. § 102(b).

Applicants have amended claims 1 to more distinctly claim the subject matter of the invention. Specifically, applicants have amended claim 1 to recite DNA sequences capable of encoding a domain or fragment of an antibody which comprises an exposed interface. Support for use of the term "antibody" can be found throughout the specification, for example, on page 4, line 30 - page 5, line 12. Support for the "exposed interface" can be found in the specification, for example on page 7, first full paragraph. Claim 1 has been further amended to recite that the interface allows contact along a longitudinal axis between adjacent domains within the heavy chain or within the light chain of the antibody (support for this aspect can be found in the specification, for example, on page 4, line 19 - page 5, line 4), and wherein the exposed interface comprises a modification resulting in increased hydrophilicity of the domain or fragment of the antibody (support for this aspect can be found in the specification, for example on page 5, lines 23-31).

Applicants have amended claims 2-4 to remove claim language which was made redundant by the amendment to claim 1.

Applicants have canceled, without prejudice, claim 6.

Applicants have amended claims 23-25 to delete the term "association" and substitute therefor the term "dimerization".

Support for this amendment can be found in the specification, for example, on page 10, line 26 - page 11, line 4.

None of these amendments contain new matter.

Claim Objections

35 U.S.C. § 132

The Examiner has objected to the amendments to the specification filed September 19, 2000 contending that they introduce new matter. Applicants have amended the specification herein to delete the objected to amendments, thereby obviating the objection. Applicants therefore request that the Examiner reconsider and withdraw the objection under 35 U.S.C. § 132.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 1-7, and 13-27 stand rejected under 35 U.S.C. § 112, first paragraph because the Examiner contends that these claims are not enabled by the specification. Specifically, the Examiner has maintained the rejection regarding these claims, contending that "the examples are on antibody derived molecules and not on any other type of immunoglobulin superfamily member which have distinctly different structures, properties and functions from antibody members...." Applicants traverse based on the amendments presented herein.

Applicants have amended claim 1 to recite DNA sequences capable of encoding modified domains and fragments of antibodies. Although applicants maintain their arguments for broader scope as detailed in the September 19, 2000 Amendment and Reply, for the sake of expediting allowance of the pending claims, applicants have limited the claims to recite modified domains and fragments of antibodies. Based on applicants' exemplification of antibody derived molecules (as noted by the Examiner) and the support and arguments described in detail in the September 19, 2000 Amendment and Reply, applicants submit that amended claim 1 is fully enabled by the specification.

Claim 1 stands additionally rejected because the Examiner contends that there is no support for the previous amendment regarding the ability of the domain or fragment to bind antigen. Although applicant believes the statement did have support in the specification as filed, applicant has obviated this rejection by deleting this recitation from the pending claims.

Claim 1 stands further rejected because the Examiner contends that there is no support for the recitation "contiguously". Although applicants disagree with this rejection and believe that support can be found in the application (for example, on page 6, lines 7-8), applicants have obviated this rejection by deleting the recitation form the pending claims.

In view of the amended claims, applicants request that the Examiner withdraw the rejections under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 102(b)

The Examiner has maintained her rejection of claims 1-7, 10, 13-17, and 26-27 under 35 U.S.C. § 102(b) as being anticipated by Johnson et al. (WO92/01787) ("Johnson"). Specifically, the Examiner reiterates that Johnson teaches "an analogue of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily, in which said analogue one or more interface amino acid residues of the domain is altered" such that the anologue is more hydrophilic than the unaltered domain. In light of the amended claims and the arguments presented herein, applicants traverse the relevance of Johnson to the instant claims.

In response to applicants arguments in the September 19, 2000 Amendment and Reply, the Examiner noted that "Johnson also teaches said alterations in contiguously adjoined domains such as those found in single chains (sic) antibodies in which the VL and VH domains are recombinantly joined contiguously...." The instant claims, however, have been amended herein to specify that the interface allows contact along a longitudinal axis between adjacent domains within the heavy or within the light chain of a larger antibody. This is distinct from Johnson's teachings, as

discussed by the Examiner, wherein the interface, although perhaps technically existing between domains which are "adjoined", nevertheless exists between immunoglobulin domains derived from different chains (i.e. VH from the heavy chain and VL from the light chain). Applicants' amended claims do not encompass this situation, as the interface must exist between domains of an individual immunological chain (i.e. either heavy or light).

Thus, based on the amendment to claim 1 presented herein, it is apparent that Johnson does not teach the types of modifications contemplated by the instant invention. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

35 U.S.C. § 103

The Examiner has maintained her rejection of claims 1-7, 10, 13-17, 18-22, and 26-27 under 35 U.S.C. § 103(a), contending that the claims are unpatentable over Johnson in view of Jenkins et al. (PNAS 92:6057-6061, 1995) ("Jenkins") and Knappik et al. (Biotechniques 17(4): 754-761, 1994) ("Knappik"). Specifically, the Examiner contends that Jenkins and Knappik provide the teaching that Johnson lacks with respect to claims 18-22. Applicants traverse.

As described above, Johnson does not teach or suggest applicants' instant invention. Further, the combination of

Jenkins or Knappik, which the Examiner cites for teaching additional moieties, adds nothing to make up for the lack of teaching in Johnson regarding the underlying DNA sequence itself. For this reason, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Conclusion

For all of the above reasons, reconsideration and allowance of the pending claims is requested.

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, D.C. 20231 on

March 5, 2002

Claire [illegible]

Signature of Person Signing

Appendix A

1. (Three times amended) A DNA sequence capable of encoding a [modified immunoglobulin superfamily (IgSF)] domain or fragment of an antibody, wherein said [modified IGSF] domain or fragment comprises an exposed interface wherein: [retains the ability to bind antigen and differs from a parent IgSF domain or fragment in that a region which comprised or would comprise an interface with a second domain contiguously adjoined to said parent IgSF domain or fragment within the chain of a larger IgSF fragment or protein is made more hydrophilic by modification]

a) said interface allows contact along a longitudinal axis between adjacent domains within a heavy chain or within a light chain of a larger antibody fragment or full antibody;

b) said exposed interface comprises a modification as compared to a domain or fragment of a parent antibody, wherein said modification to said exposed interface results in said domain or fragment of said antibody demonstrating increased hydrophilicity as compared to said domain or fragment of said parent antibody.

2. (Twice amended) The DNA sequence according to claim 1 in which said modification is a substitution of one or more amino acids [at said region which comprised or would comprise the interface] with amino acids which are more hydrophilic.

3. (Twice amended) The DNA sequence according to claim 1 in which said modification [is] comprises:

(a) insertion of one or more hydrophilic amino acids; [in said region which comprised or would comprise the interface, or]

(b) insertion of one or more amino acids; [which increase the overall hydrophilicity in said region which comprised or would comprise the interface, or]

(c) deletion of one or more hydrophobic amino acids; or [in said region which comprised or would comprise the interface, or]

(d) deletion of amino acids[, said deletion leading to an increase in the overall hydrophilicity in said region which comprised or would comprise the interface].

4. (Twice amended) The DNA sequence according to claim 1 in which said modification consists of any two or more of:

a) substitution of one or more amino acids [at said region which comprised or would comprise the interface] with amino acids which are more hydrophilic;

b) insertion of one or more hydrophilic amino acids [in said region which comprised or would comprise the interface,] or insertion of amino acids; and [which increase the overall hydrophilicity in said region which comprised or would comprise the interface]

c) deletion of one or more hydrophobic amino acids [in said region which comprised or would comprise the interface,] or deletion of amino acids[, said deletion leading to an increase in the overall hydrophilicity in said region which comprised or would comprise the interface].

23. (Amended) The DNA sequence according to claim 20 in which said peptide comprises a dimerization [an association] domain which results in self-association of two or more of said antibody fragments.

24. (Amended) The DNA sequence according to claim 23 in which said dimerization [association] domain is derived from a leucine zipper or from a helix-turn-helix motif.

25. (Amended) The DNA sequence according to claim 20 in which said peptide comprises a first dimerization [association] domain which results in hetero-dimerization[association] of one or more of said antibody fragments with one or more peptides or proteins comprising a second hetero-dimerization[association] domain being able to dimerize [associate] with said first hetero-dimerization [association] domain.